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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/457,771	12/09/99	EMANUELE R	19720-0624

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	10

DATE MAILED: 11/21/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

FILE COPY

Office Action Summary

Application No.	Applicant(s)
09/457,771	Emanuelle et al
Examiner	**Group Art Unit**
Richard Schnizer	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-16 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-16 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Continued Prosecution Application

The request filed on 7/28/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/457,771, is acceptable and a CPA has been established. An action on the CPA follows.

Claim Rejections - 35 USC § 112

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions which can alter gene activity, such as are known in the art (e.g. Allison et al US Patent 4,772,466,), and for intramuscular delivery and expression of nucleic acids *in vivo* as is known in the art (e.g. Simons et al, 1992), does not reasonably provide enablement for therapeutic delivery of any and all nucleic acids *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant's claims are broadly directed to compositions comprising block copolymers and compounds which can alter gene activity. The compounds may be nucleic acids. The claimed invention broadly encompasses the transfer of genes, oligonucleotides, antisense oligonucleotides, and RNA into any and all cell types, tissues, and animals, including humans. The claims specifically recite that the compositions are therapeutic, thus the compositions must be enabled for

therapeutic use. Claims 9-16 are directed to methods of delivering compounds, such as nucleic acids, which can alter gene activity. The only disclosed purpose of such methods is gene therapy.

Factors to be considered in the determination of enablement include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Considerations for any gene therapy protocol include, for example, the choice of target gene and tissue, dosage and route of administration, the efficiency of gene transfer the level and duration of gene expression or inhibition necessary to exert a therapeutic effect, the action of complement and the immune system, as well as nucleases and proteases in the circulation, and safety issues including the toxicity of the delivery system and possible oncogenic transformation. Applicant has claimed a broad range of block copolymer compositions but has not supplied sufficient guidance for one of skill in the art to choose a specific copolymer composition, in terms of the molecular weight of the polyoxypropylene (POP) component, the percentage weight of polyoxyethylene (POE), or the amount of surfactant or alcohol included. It is not made clear if the choice of these parameters is critical to the success and predictability of the invention, or if all of the copolymers in the claimed range will produce therapeutic benefit *in vivo*.

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH

Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concludes, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

The state of the art with respect to antisense therapies is set forth by Crook (In Basic Principles of Antisense Therapeutics, Springer-Verlag, Eds, New York, pgs. 1 and 4), who teaches that although antisense techniques have progressed rapidly, "the technology remains in its infancy", and the utility of the approach is still debatable (pg. 1, Introduction). Crook points out several factors which may influence the biological effect of an antisense oligonucleotide (AODN), including the rate of uptake of the AODN, rate of distribution within the target cell, stability within the target cell, local concentration of the oligonucleotide, and the concentration and stability of the target mRNA (pgs. 1 and 4). Furthermore, Branch (Trends in Biochem Sci 23:

45-50, 1998) teaches that selection of appropriate antisense sequences is difficult because secondary structures of mRNAs *in vivo* frequently restrict access of antisense oligonucleotides to the target sequence (page 45, col. 3. first para., page 48, last para. and page 49). Branch states, "Since accessibility cannot be predicted, rational design of antisense molecules is not possible" (page 49, col. 2, last para.). These concerns are relevant to all therapies which depend on antisense technology, *e.g.* triple helix-forming oligonucleotides, ribozymes, and inhibitory antisense oligonucleotides.

The specification discloses a working example of genetic immunization (Example XIII) in which mice were injected with compositions comprising either of two copolymers of the invention and plasmid DNA comprising either of two HSV genes (gB or gD). The mice were boosted at 3-4 week intervals and subsequently challenged with 2.4 $X10^4$ pfu of HSV. Control animals which received no plasmid and no copolymer died, whereas those animals which received the composition survived. It is noted that this example appears in one parent application, 09/104,088, filed 6/24/98, but does not appear in earlier parent applications (08/926,297, filed 9/5/97; 08/725,842, filed 9/30/96; or 08/138,271, filed 10/15/93). At the time of the invention, genetic immunization was not practiced with routine success by those of skill in the art. Donnelly et al (J Immunol. Meth. 176:145-152, 1994) teach that, in 1994, genetic immunization with naked DNA had "[p]otential clinical applications", but its utility for treating bacterial diseases remained to be demonstrated, and therapeutic uses of DNA vaccines in general were only beginning to be explored. See page 150, column 1, first full paragraph. Donnelly further teaches that, in selected

animal models where challenge studies can be performed, [genetic] immunization may provide protective immunity". And "[t]he extent to which this method can be applied to proteins not of vertebrate origins, e.g. antigens from bacteria and protozoan parasites, remains to be determined." See page 150, column 2, first full paragraph. Based on these teachings, it is clear that at the time of the invention, the process of genetic immunization was in its infancy, and was an unpredictable process which was not practiced with routine success by those of skill in the art. The process of obtaining therapeutic effects, as required by the instant claims, is considered to be even more unpredictable, and does not appear to have been achieved prior to the time of filing.

The specification discloses no other example of therapeutic nucleic acid delivery. For example, no example or guidance is provided for such therapeutic approaches as delivery of nucleic acids encoding therapeutic enzymes, antisense oligonucleotides, oligonucleotides intended to form triple helices, or ribozymes. Finally, no example of the alteration of the activity of any specific gene is presented.

In view of the unpredictability of the art of therapeutic nucleic acid, the breadth of the claimed therapeutic nucleic acids, the absence of any working example at the time of filing, and the absence of any guidance with regard to the therapeutic use of oligonucleotides, ribozymes, or genes encoding therapeutic enzymes, one of skill in the art would be unable to practice the invention commensurate in scope with the claims without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 15 contain the trademark/trade name Tween 80. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe surfactant intended to have particular characteristics and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

(g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Claims 1-4, 6, 9-12, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Allison et al (US Patent 4,772,466, issued 9/20/88).

Allison teaches a composition comprising an immunologically effective amount an antigen and block copolymer composed of POE and POP moieties. Preferred embodiments include a copolymer comprising a POP constituent of from 3250-4000 molecular weight, and about 10-20% (w/w) POE. See column 4, lines 19-23. The composition may also comprise 0.5%-2.5% (w/w) TWEEN 80, and 1%-30% (w/w) alcohol. The alcohol may be from 6-30 carbon atoms in length. See column 6, lines 45-53, and column 9, lines 26-29; and column 10, lines 24-28. It is noted that the range of 1-30% (w/w) overlaps the claimed range of 0.5%-5% (v/v) because the density of alcohols is slightly less than that of water. Allison also teaches a method of using the composition to cause an immune response. By definition, an immune response requires alterations in gene activity, *e.g.* the production of antibodies. See column 11, lines 60-67.

Claims 1-16 are rejected under 35 U.S.C. 102(e) and 102(g) as being anticipated by Emanuele et al (US Patent 5,567,859, issued 10/22/96).

Emanuele teaches a composition comprising a block copolymer composed of POE and POP moieties, as well as either antibiotics, or antisense oligonucleotides, triplex DNA compounds, or ribozymes. See column 1, lines 48-53; and column 2, lines 1-6. Preferred embodiments include a copolymer comprising a POP constituent of from 2250-4000 molecular weight, and about 10-30% (w/w) POE. See column 2, lines 55-62. The composition may also comprise 2% (w/w) TWEEN 80, and 1% (w/w) ethanol. See column 9, lines 2-4. It is noted that this composition, while not enabled for therapeutic use of nucleic acids, is enabled for delivery of nucleic acids *in vivo,* and for therapeutic delivery of antibiotics. Delivery of antibiotics would be expected to indirectly alter the expression of genes associated with immune response by eliminating the infectious agents.

Thus Emanuele anticipates the claims.

The rejection under 35 U.S.C. 102(g) is made because, although the specification of Emanuele discloses the same invention as that disclosed in the instant application, the inventorship is not identical. Thus it is unclear precisely who has invented the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 8-14, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simons et al (1992) Nature 359:67-70; in view of Allison et al, U.S. 4,772,466, and Robinson-Benion et al (Antisense Research and Development, 1(1): 21-33, 1991).

Simons teaches the delivery of antisense c-myb oligonucleotides to rat arterial smooth muscle cells by the application of a composition of antisense oligonucleotide and a block copolymer (Pluronic (TM) gel), for the purpose of inhibiting gene expression and cell proliferation. Simons used Pluronic (TM) F-127, which has a POP molecular weight of about 4000, and is 70% POE by weight. Simons does not teach a block copolymer comprising less than 50% POE by weight, or an expression vector.

Allison teaches a composition comprising an immunologically effective amount an antigen and block copolymer composed of POE and POP moieties. Preferred embodiments include a copolymer comprising a POP constituent of from 3250-4000 molecular weight, and about 10-20% (w/w) POE. See column 4, lines 19-23. The composition may also comprise 0.5%-2.5% (w/w) TWEEN 80, and 1%-30% (w/w) alcohol. The alcohol may be from 6-30 carbon atoms in length. See column 6, lines 45-53, and column 9, lines 26-29; and column 10, lines 24-28. It is noted that the range of 1-30% (w/w) overlaps the claimed range of 0.5%-5% (v/v) because the density of alcohols is slightly less than that of water. Allison also teaches a method of using the

composition to cause an immune response. By definition, an immune response requires alterations in gene activity, *e.g.* the production of antibodies. See column 11, lines 60-67.

Robinson-Benion teaches a vector designed to express antisense RNA which suppresses the expression of c-fos, and suggests the use of this antisense inhibition to analyze the mechanism of transcriptional repression *in vivo*.

It would have been obvious to substitute the block copolymer of Allison for the block copolymer of Simons. One would have been motivated to do so because such compounds can be considered analogous or homologous. That is, they are sufficiently structurally similar that there is a presumed expectation that they will possess similar properties. See MPEP 2144.09, and In re Wilder , 563 F.2d 457, 195 USPQ 426 (CCPA 1977). It wold have been similarly obvious to substitute the expression vector of Robinson-Benion for the antisense oligonucleotides of Simons et al in order to study the mechanism of c-fos transcriptional repression *in vivo*, as suggested by Robinson-Benion.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM

and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Richard Schnizer, Ph. D.

Karen M. Hauda
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